HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2022 September 08.

Published in final edited form as:

Pediatr Blood Cancer. 2015 October ; 62(10): 1819–1825. doi:10.1002/pbc.25544.

Racial/Ethnic and Socioeconomic Disparities in Survival Among Children With Acute Lymphoblastic Leukemia in California, 1988–2011: A Population-Based Observational Study

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Abstract

Background.—Despite advances in treatment, survival from acute lymphoblastic leukemia (ALL) remains lower among non-White children than White children in the US. We investigated the association of race/ethnicity and socioeconomic status (SES) with survival.

Procedures.—We analyzed 9,295 Californian children (3,251 Whites, 4,890 Hispanics, 796 Asians, and 358 Blacks) aged ≤ 19 years diagnosed with a first primary ALL during 1988–2011. We used the Kaplan–Meier method to estimate survival at 1, 5, and 10 years after diagnosis for three calendar periods. Hazard ratios of death for race/ethnicity, SES, and clinical factors were estimated by Cox regression models.

Results.—Median follow-up time was 7.4 years (range 0–25 years). Over time, survival after ALL improved steadily, but inequalities persisted across races/ethnicities. Five-year survival (95%

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Author Contribution

RA and DYL performed and RK advised on the statistical analyses. DYL, RCR, SLG, RK, RMG, and NMM interpreted the data and drafted and critically reviewed the manuscript. RA and THMK designed the study, interpreted the data, and led the writing and review of the manuscript. All authors read and approved the final manuscript.

Conflict of interests: Nothing to declare.

confidence interval) was 85.0% (83.6–86.2) for White, 81.4% (78.3–84.0) for Asian, 79.0% (77.8–80.2) for Hispanic, and 74.4% (69.4–78.8) for Black children. In multivariable-adjusted models, the hazard of death was increased by 57% among Black, 38% among Hispanic, and 33% among Asian children compared with White children. Patients residing in the lowest SES neighborhoods at diagnosis had a 39% increased risk of death relative to those living in higher SES neighborhoods.

Conclusion.—Despite significant improvements in survival, non-White children and children residing in low SES neighborhoods experienced worse survival even after adjusting for potential confounders. Our findings highlight the need to capture specific information on disease biology, treatment, and treatment adherence to better understand the predictors of lower survival in minority and low SES groups.

Keywords

childhood; leukemia; population-based; race/ethnicity; SES; survival

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric neoplasm and the leading cause of death due to disease in children and adolescents aged 1–19 years in the United States (US).[1] Several studies have reported an increase in the incidence of childhood ALL in Europe [2] and the US.[3] Evidence suggests that there may be an inherited genetic predisposition to this disease among different races/ethnicities.[4] Strikingly, genetic factors that increase the susceptibility to ALL appear also to be associated with drug-resistant ALL phenotypes and might, in part, explain the poor survival in certain ethnic groups.[5]

Survival from childhood ALL represents one of the most successful advances in the history of science and medicine. ALL was consistently fatal until the 1950s; however, currently approximately 90% of children can be cured in developed countries.[6] This progress has been attributed largely to the use of effective chemotherapy regimens of variable intensities that are adapted to precise risk stratification and assessment of early treatment response.[6]

Despite the dramatic improvement in the survival of children with ALL in the last four decades, survival has varied widely by race/ethnicity in developed [7] and developing nations.[8] Non-adherence to treatment, lack of access to care, cultural influences, socioeconomic status (SES), and biologic features have been implicated in these variations.[9] However, the extent to which these factors contribute to survival inequalities remain unclear.

California has the largest and most racially and ethnically diverse population in the US [10] and it has maintained a statewide high-quality, population-based cancer surveillance system since 1988. In this study, we examined how survival after ALL varied by race/ethnicity, SES, and clinical factors in Californian children over a 24-year period. Our population-based study on childhood ALL simultaneously investigates the association of race/ethnicity, neighborhood SES, health insurance, type of treating facility, treatment, and secondary

neoplasms as well as factors examined previously (e.g., age, gender, immunophenotype, and calendar period).

METHODS

Patients and Study Design

For this population-based observational study, data were retrieved for children and adolescents aged 0–19 years residing in California when diagnosed with a first, primary ALL from January 1, 1988 through December 31, 2011, and followed for vital status through December 31, 2012. Data were obtained from the California Cancer Registry (CCR), to which all new cases of cancer diagnoses must be reported by state law. The CCR contributes to approximately half of the data in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) and is estimated to include more than 99% of all invasive cancers diagnosed in California. We included the following morphology codes from the *International Classification of Diseases for Oncology*, third edition (ICD-O-3):[11] 9,727, 9,728, 9,729, 9,811, 9,812, 9,813, 9,814, 9,815, 9,816, 9,817, 9,818, 9,835, 9,836, and 9,837. Among 9,429 eligible patients, 9,295 were included for survival analysis. The following patients were excluded from analysis: 7 reported by death certificate only (DCO), 5 reported by autopsy only, 51 for whom race/ethnicity was unknown, 60 of Non–Hispanic American Indian (NHAI) race/ethnicity for whom the small sample size precluded analysis, and 11 with inconsistent dates of diagnosis or follow-up and/or leukemia classification. ALL was morphologically verified in 99.8% of patients, and the percentage of cases with verified vital status on December 31, 2012, was 87.1%.

Institutional review board (IRB) approval—Ethics approval for human subjects research was obtained from the California Prevention Institute of California Institutional Review Board. As the analysis was based on state-mandated cancer registry data, the study was conducted in accordance with the waivers of individual informed consent and HIPPA authorization.

Covariates

Covariates included in the analysis were age at diagnosis (<1, 1–4, 5–9, 10–14, and 15–19 years); gender (male, female); race/ethnicity (Non-Hispanic White [White], Non-Hispanic Black [Black], Hispanic, and Non-Hispanic Asian/Pacific Islander [Asian]); immunophenotype (categorized as B-cell, T-cell, or not otherwise specified [NOS] according to the morphology codes); secondary neoplasms; and neighborhood SES. Secondary neoplasm was defined as a new malignancy registered in the CCR after the diagnosis of ALL, following the SEER's multiple primaries rules for hematopoietic diseases.[12] Some types of malignant neoplasms have been associated with worse prognosis [13] and we have controlled for their occurrence in our analyses. Because information on SES at the individual level is not collected by the CCR, a previously developed neighborhood SES measure [14] was used. It is derived from principal components analysis of seven census indicator variables of SES (education level, proportion unemployed and with a blue collar job, proportion below 200% of federal poverty level, and median household income, rent, and home value). This index is based on data at the level of the census block groups and is considered adequate as a surrogate to SES at individual level,[15]

and can capture neighborhood-level factors that may affect cancer incidence and outcomes.[16] SES was divided into quintiles based on the statewide distribution and assigned to patients on the basis of their residence at time of diagnosis. Other covariates included type of insurance at time of initial treatment (private, public, no insurance, or unknown) collected from 1996 onwards; calendar period (1988–1995, 1996–2003, 2004–2011); and type of treating hospital. Because the care provided by specialized pediatric oncologic centers may be different from that provided in general hospitals, we identified children's hospitals and pediatric cancer centers in California by using listings from the Children's Hospital Association [17] and the Children's Oncology Group (COG).[18] These hospitals offer clinical trials sponsored by the COG, which is supported by the NCI. On the basis of the cancer reporting facility, patients were classified by whether they had received care at a pediatric cancer center (yes, no). Chemotherapy, radiotherapy, and time to chemotherapy were evaluated in descriptive analyses of treatment. They were not included in the statistical model because of changes in the use of central nervous system (CNS) radiation over time [19] and the widespread use of chemotherapy protocols. Inclusion of treatment in the model did not change the associations observed among race/ethnicity, SES, and survival.

Statistical Analyses

We used the χ^2 test to compare frequency distributions of sociodemographic and clinical characteristics by race/ethnicity. Follow-up time was defined as the date of diagnosis to the date of death from any cause, or censoring at the end of the study period (December 31, 2012) or last known date of follow-up, whichever came first.

We estimated overall survival at 1, 5, and 10 years for each covariate (except chemotherapy and radiation) and calendar period by the Kaplan–Meier method. The log-rank test was used to compare differences in survival across strata. We used unadjusted and multivariable-adjusted Cox regression models to estimate the hazard ratios (HRs) of death with associated 95% confidence interval (CI).

We tested the proportional-hazards assumption by examining log–log survival plots and confirmed the results by using Schoenfeld residuals. There was evidence that age, immunophenotype, and secondary neoplasms violated the proportional hazard assumption, and these were therefore included as stratification variables in the models. Secondary neoplasm was analyzed as a time-dependent variable.

Because information on type of insurance was not routinely collected prior to 1996, we ran three Cox regression models: a model without insurance with all patients, a model without insurance but limited to patients diagnosed from 1996 onwards, and another model including insurance but limited to patients diagnosed from 1996 onwards. We investigated interactions between racial/ethnic groups and other covariates. Statistical analyses were performed by using the Stata 13 software and a two-sided P-value < 0.05 was considered statistically significant.

RESULTS

Sociodemographic and Clinical Characteristics

Table I shows patients and disease characteristics by race/ethnicity. In the 9,295 patients in our cohort, there was a higher percentage of males (58%) than females (42%). More than half the patients (52%) were Hispanic, followed by White (35%), Asian (9%), and Black (4%). The median age at diagnosis was 4 years for Asian, 5 years for White and Hispanic, and 7 years for Black children. By immunophenotype, 60% of patients had B-cell, 12% had T-cell, and approximately 28% had NOS ALL. The proportion of T-cell ALL was significantly higher in Black (23%) than in White (15%), Asian (13%), and Hispanic (10%) children. White and Asian children were more likely to have private insurance (80% and 74%, respectively) than Black and Hispanic children (53% and 40% respectively). Approximately 1.4% of children were diagnosed with secondary neoplasms, of which 58% were solid and 46% were hematopoietic. The use of CNS radiation decreased progressively from 24% in the first time period to 12% in the last period. Chemotherapy was administered to more than 98% of children, of whom at least 95% received chemotherapy within 2 weeks of diagnosis.

Survival

Table II displays survival probabilities at 1, 5, and 10 years, by sociodemographic and clinical characteristics. Figures 1 and 2 show survival by race/ethnicity and SES, respectively. The median follow-up time was 7.4 years (range 0–25 years). By the end of the study period, 1,955 study patients died. Survival improved steadily over calendar time but was persistently lower for Black, Hispanic, and Asian children than for White children. Differences in survival were most striking between Black and White children.

Unadjusted and Multivariable Analyses

In the unadjusted model all variables were associated with significant increased hazard of death. After multivariable adjustment, our analysis revealed that the HRs of death were still significant for race/ethnicity and SES (Table III). The hazard of death was increased by 57% (HR = 1.57 [1.26–1.96]) among Black, 38% (HR = 1.38 [1.23–1.55]) among Hispanic, and 33% (HR = 1.33 [1.12–1.59]) among Asian children compared with White children. Patients residing in the lowest SES neighborhoods were at 39% (HR = 1.39 [1.18–1.64]) increased risk of death than those in the higher SES neighborhoods. After controlling for other covariates, the hazard of death was not associated with the type of hospital in which children were treated or with type of insurance for patients diagnosed from 1996 onwards. Insurance minimally attenuated the HRs for race/ethnicity and SES among patients diagnosed from 1996 onwards (Table III). In addition, the inclusion of SES in our model did not substantially change the racial/ethnic differences in survival that we observed. There were no significant interactions between race/ethnicity, SES, calendar period, and other study covariates.

DISCUSSION

In our large population-based study of nearly 10,000 children with ALL, survival for Black, Hispanic, and Asian children was lower than that for White children. The survival differences we observed in our cohort persisted over time and were most marked between Black and White children. In contrast to previous studies reporting that survival of Asian children was similar to [20] or better [21] than for White, Hispanic, and Black children, our study showed that Asian children in California had lower survival than White children with ALL. Our results are consistent with a previous study [7] that also used US population-based data, but we extended their findings by additionally investigating neighborhood SES, secondary neoplasms, type of insurance, treatment, and treating facility.

Genetic and non-genetic factors help to explain disparities in cancer survival. Our population-based study allowed the investigation of non-genetic factors and found that neighborhood SES had a significant, independent association with survival, particularly when comparing children residing in the highest and lowest SES neighborhoods. The inclusion of SES in our statistical model did not substantially change the racial/ethnic differences in survival that we observed, suggesting that other factors underlie these survival disparities. Our SES finding is consistent with previous studies of poorer survival among financially deprived populations.[22]

White and Asian children were more likely than Hispanic and Black children to have private insurance, but the type of insurance did not significantly affect survival after ALL after adjustment for other variables. Insurance may have not been associated with survival because, in California, patients younger than 21 years are eligible for California Children's Services (CCS), a state program that offers insurance for chronic and complex diseases and covers all children with cancer with or without insurance. Although the CCS program ensures that all children with ALL have access to care, this may not be sufficient in the long-term for children with low SES. Differences in relapse rates among children from different racial/ethnic groups have been observed. In a study on adherence to oral 6-mercaptopurine during the maintenance phase of ALL treatment, non-adherence was significantly higher among non-White children than White children and it considerably increased relapse rates. Sociodemographic characteristics also played a significant role in adherence to treatment. [22]

Although past evidence suggests that children with ALL treated at specialized pediatric cancer centers had better survival than those at general hospitals,[23] our study did not find survival differences by treating facility. Because the treating facility typically refers to the hospital that initially diagnosed and/or treated the patient, it is possible that some children admitted in non-specialized pediatric hospitals were later referred to pediatric cancer centers where standardized COG protocols were used, thus confounding our results.

ALL is a lethal disease if treatment is not started promptly. Although the lack of appropriate chemotherapy agents might contribute to the lower survival in Eastern Europe,[24] our examination of the proportion of children treated with chemotherapy and time from diagnosis to the start of treatment showed that the majority of study patients were treated

within the first 2 weeks of diagnosis. However, late diagnosis might have had an adverse effect on outcome. Parents who are undocumented immigrants or of lower SES may wait longer to seek medical care for their children or may do so when the child is already severely sick. Late diagnosis may increase the risk of (early) death [25–27] because patients may develop severe infectious and/or metabolic complications prior to referral to a specialized cancer center.[28] However, we did not have sufficient information to evaluate this possibility.

Our data indicate that the use of prophylactic cranial irradiation has decreased markedly over time, suggesting protocol adherence to the new recommendations for using systemic and intrathecal therapy instead of radiation for children with high-risk CNS relapse. This recommendation aims to prevent late radiation-related complications such as second neoplasms.[29] Infants and older children had significant lower survival than did children aged 1–9 years, supporting findings in previous studies in Europe [30] in the US.[1]

The treatment of childhood leukemia is complex, expensive, and lengthy (2.5–3 years). With modern supportive care, fewer than 10% of deaths among children with ALL are due to therapy-associated toxicity,[31] and disease relapse remains the leading cause of death.[32] Although relapsed ALL is treated with curative intent in the US, the long-term survival of children who relapse is only approximately 25%, even when bone marrow transplant is available.[32] Multiple factors might affect the survival of children with ALL, and this can be a complex construct involving socioeconomic and cultural variables.[22]

Differences in disease biology may explain, in part, the persistent gap in survival by race/ethnicity. For example, in our study, survival differences were more marked between Black and White children (Fig. 1, Table II). Intrinsic biologic features may partially explain this observation. Previous studies reported that compared to White children, Black children with ALL had a higher incidence of unfavorable features, including high leukocyte count, higher proportion of T-cell leukemia, chromosome translocations [e.g. t(1,19)], and molecular abnormalities associated with an increased risk of relapse.[33] In contrast, approximately 50% of White children have ALL with favorable genetic features (B-cell ALL), which translate to excellent prognosis.[4] Pui et al.[34] reported that survival rate of Black children receiving intensive risk-based therapy and comprehensive supportive care can be similar to that of White children, thereby reducing the impact of these adverse factors. However, to our knowledge, these results found at a single institution, have not been replicated.

Intrinsic biologic differences may also play an important role in the poor prognosis of ALL among Hispanic children. A recent review [9] of the genomic profiling of ALL associated with susceptibility and outcome among Hispanic children identified a novel subtype of ALL called Philadelphia chromosome-like (Ph-like) ALL among these children. The incidence of Ph-like ALL in Hispanic children is significantly higher (35%) than in non-Hispanic children (7%). Approximately 50% of children with this subtype overexpress the somatic cytokine receptor-like factor 2 (*CRLF2*).[33] Furthermore, Perez-Andreu et al.[35] demonstrated that inherited GATA binding protein 3 (GATA3) variants are also overrepresented among Hispanics and increase the susceptibility to Ph-like ALL. The

presence of both these variants is associated with a higher risk of relapse among Hispanic children with ALL and may in part explain their poor response to treatment.

Our study has some limitations. Data on specific genetic abnormalities have only been collected by the CCR since 2010. Because of the small size of this group, we could not compare the survival of children on the basis of genetic characteristics. However, this will be of interest in future studies. Most children and adolescents with ALL in California are treated at pediatric cancer centers that use COG protocols, but we do not have information about which patients are treated with these protocols and the intensity of treatment administered. We lacked data on relapse rates, as disease recurrence is not routinely collected by population-based cancer registries.

The strengths of our study include the use of a high-quality population-based dataset, a large sample of an ethnically and racially diverse population, and long period of post-diagnostic observation that allowed us to examine trends in outcome. Our study covered nearly the entire population of children and adolescents diagnosed with ALL in California and provided information on numerous factors such as neighborhood SES, insurance, treatment, treating facility, secondary neoplasm, and immunophenotype as well as age, gender, and calendar period.

In summary, despite the remarkable improvement in cure rates after ALL, non-White children and children in low SES neighborhoods have been disproportionally dying even when access to high-quality care is available and standardized protocols are followed. In the coming years, genomic findings will dramatically change the prognostic classification of ALL. In the era of precision medicine, the value of population-based cancer registries can be improved by collaborating with pediatric oncologists and cancer registries from COG-affiliated hospitals. Capturing specific biologic (e.g., ALL genomic signature, minimal residual disease, blast chromosomal abnormalities, presenting white counts, and NCI risk grouping), and socioeconomic (e.g., treatment adherence) information can help to identify predictors of racial/ethnic differences in treatment failure and guide the development of interventions aimed at improving survival for minority and low SES children with ALL.

ACKNOWLEDGEMENTS

The authors thank Michel P Coleman (LSHTM) for the early contribution to this project, Shawky Matta and Kathleen Davidson-Allen (CPIC) for their expertise with cancer registry data, and Vani Shanker (SJCRH) for manuscript editing.

Grant sponsor: Children with Cancer UK; Grant sponsor: Cancer Center Support (CORE), National Institutes of Health P30; Grant number: CA021765-30; Grant sponsor: American Lebanese Syrian Associated Charities (ALSAC); Grant sponsor: Stanford Cancer Institute (SLG); Grant sponsor: California Department of Public Health; Grant number: U58DP003862-01; Grant sponsor: California Health and Safety Code Section; Grant number: 103885; Grant sponsor: Surveillance, Epidemiology, and End Results (SEER); Grant sponsor: National Cancer Institute (NCI); Grant number: HHSN261201000140C; Grant sponsor: Cancer Prevention Institute; Grant number: N01-PC-35136; Grant sponsor: Public Health Institute; Grant numbers: N02-PC-15105; U55/CCR921930-02; HHSN261201000034C; Grant sponsor: University of Southern California; Grant number: HHSN261201000035C; Grant sponsor: Disease Control and Prevention's National Program

Abbreviations:

ALL	acute lymphoblastic leukemia

CCR	California cancer registry
CCS	California children's services
COG	children's oncology group
CI	confidence interval
CNS	central nervous system
CRLF2	cytokine receptor-like factor 2
DCO	death certificate only
HR	hazard ratio
ICD-O-3	international classification of diseases for oncology, third edition
NCI	national cancer institute
NHAI	non-hispanic American Indian
NOS	not otherwise specified
SEER	surveillance, epidemiology, and end results
SES	socioeconomic status
US	United States

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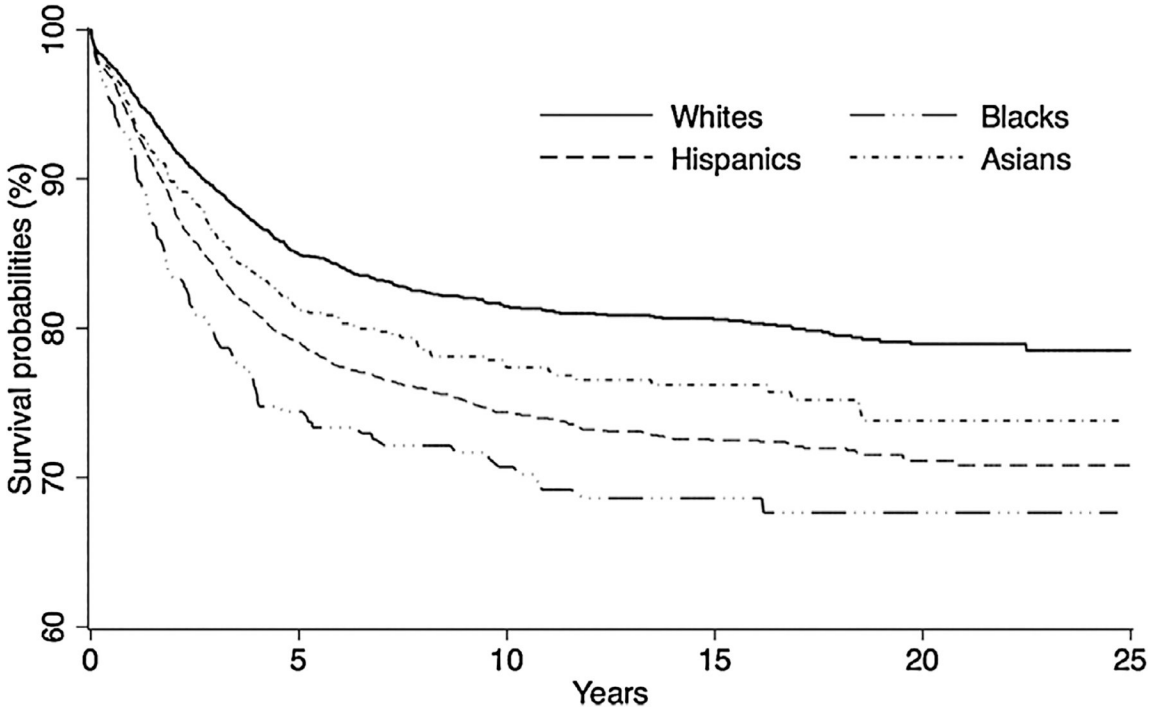

Fig 1.

Overall survival by race/ethnicity among children (0–19 years old) diagnosed with acute lymphoblastic leukemia in California, 1988–2011.

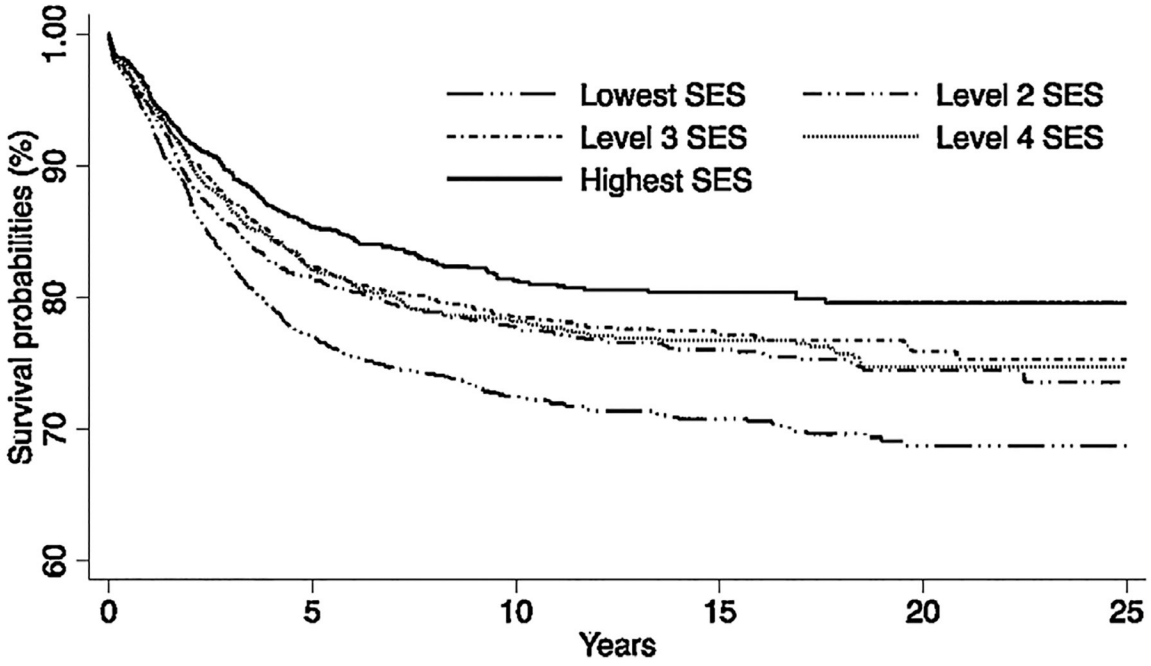

Fig 2.

Overall survival by socioeconomic status among children (0–19 years old) diagnosed with acute lymphoblastic leukemia in California, 1988–2011.

TABLE I.

Sociodemographic and Clinical Characteristics of Children (Aged 0–19 Years) With Acute Lymphoblastic Leukemia Diagnosed From 1988 to 2011 and Followed Up to 2012 in California, by Race/Ethnicity

Covariates	Whites N (%)	Blacks N (%)	Hispanics N (%)	Asians N (%)	Total cohort N (%)	P^a
Total	3,251 (35)	358 (4)	4,890 (52)	796 (9)	9,295 (100)	
Age at diagnosis, years						
<1	69 (2.1)	9 (2.5)	158 (3.2)	29 (3.6)	266 (2.9)	
1–4	1,468 (45.2)	117 (32.7)	2,023 (41.4)	382 (48.0)	3,990 (42.9)	
5–9	868 (26.7)	102 (28.5)	1,216 (24.9)	194 (24.4)	2,382 (25.6)	
10–14	465 (14.3)	74 (20.7)	807 (16.5)	101 (12.7)	1,447 (15.5)	
15–19	381 (11.7)	56 (15.6)	686 (14.0)	90 (11.3)	1,213 (13.1)	<0.0001
Median	5	7	5	4	5	
Gender						
Male	1,911 (58.8)	206 (57.5)	2,815 (57.6)	459 (57.7)	5,391 (58.0)	
Female	1,340 (41.2)	152 (42.5)	2,075 (42.4)	337 (42.3)	3,904 (42.0)	0.738
Chemotherapy						
No	44 (1.3)	11 (3.1)	79 (1.6)	7 (0.9)	141 (1.5)	
Yes	3,207(98.7)	347 (96.9)	4,811 (98.4)	789 (99.1)	9,154 (98.5)	0.031
CNS radiation						
No	2,717 (83.6)	275 (76.8)	4,085 (83.5)	687 (86.3)	7,764 (83.5)	
Yes	534 (16.4)	83 (23.2)	805 (16.5)	109 (13.7)	1,531 (16.5)	0.001
Treatment at a pediatric cancer center						
No	931 (28.6)	131 (36.6)	1,571 (32.1)	240 (30.1)	2,873 (30.9)	
Yes	2,320 (71.4)	227 (63.4)	3,319 (67.9)	556 (69.9)	6,422 (69.1)	0.001
Leukemia immunophenotype						
T-cell	483 (14.9)	84 (23.4)	464 (9.5)	102 (12.8)	1,133 (12.2)	
B-cell	1,736 (53.4)	176 (49.2)	3,183 (65.1)	490 (61.6)	5,585 (60.1)	
NOS	1,032 (31.7)	98 (27.4)	1,243 (25.4)	204 (25.6)	2,581 (27.7)	<0.0001
Secondary neoplasms						
No	3,209 (98.7)	356 (99.4)	4,838 (98.9)	782 (98.2)	9,185 (98.8)	
Yes	42 (1.3)	2 (0.6)	52 (1.1)	14 (1.8)	110 (1.2)	0.223

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Covariates	Whites N (%)	Blacks N (%)	Hispanics N (%)	Asians N (%)	Total cohort N (%)	P^a
Socioeconomic status						
1. Lowest 20%	247 (7.6)	96 (26.8)	2,067(42.2)	102 (12.8)	2,513 (27.0)	
2	532 (16.4)	109 (30.5)	1,256 (25.7)	120 (15.1)	2,020 (21.7)	
3	683 (21.0)	66 (18.4)	831 (17.0)	139 (17.5)	1,723 (18.5)	
4	847 (26.0)	58 (16.2)	479 (9.8)	200 (25.1)	1,585 (17.1)	
5. Highest 20%	942 (29.0)	29 (8.1)	257 (5.3)	235 (29.5)	1,463 (15.7)	<0.0001
Calendar period						
1988–1995	1,169 (35.9)	104 (29.0)	1,162 (23.8)	222 (27.9)	2,657 (28.6)	
1996–2003	1,093 (33.6)	127 (35.5)	1,670 (34.1)	270 (33.9)	3,160 (34.0)	
2004–2011	989 (30.4)	127 (35.5)	2,058 (42.1)	304 (38.2)	3,478 (37.4)	<0.0001
Type of health insurance: limited to cases diagnosed from 1996 onwards (N = 6638)						
No insurance	14 (0.7)	9 (3.5)	106 (2.9)	4 (0.7)	133 (2.0)	
Private insurance	1,669 (80.1)	135 (53.2)	1,493 (40.0)	425 (74.0)	3,722 (56.1)	
Public insurance	341 (16.4)	101 (39.8)	1,997 (53.6)	128 (22.3)	2,567 (38.7)	
Unknown	58 (2.8)	9 (3.5)	132 (3.5)	17 (3.0)	216 (3.2)	<0.0001

CNS, central nervous system; NOS, not otherwise specified.

[a] χ^2 *P*-value.

TABLE II.

Overall Survival With 95% Confidence Intervals for Acute Lymphoblastic Leukemia at 1, 5, and 10 Years After Diagnosis in Children (0–19 Years Old) in California From 1988 to 2011, by Sociodemographic and Clinical Factors

Covariates	1-year survival (95%CI)	5-year survival (95%CI)	10-year survival (95%CI)
All children	94.5 (94.0–95.0)	81.2 (80.3–82.0)	77.1 (76.1–78.0)
Age at diagnosis			
<1	76.9 (71.3–81.6)	50.2 (43.7–56.2)	45.7 (39.1–52.1)
1–4	97.9 (97.4–98.3)	89.3 (88.2–90.3)	86.3 (85.1–87.4)
5–9	96.6 (95.8–97.3)	86.2 (84.7–87.6)	80.7 (78.8–82.4)
10–14	91.8 (90.2–93.1)	73.5 (71.0–75.7)	69.0 (66.3–71.5)
15–19	86.3 (84.2–88.1)	60.2 (57.2–63.0)	55.8 (52.6–58.8)
Log-rank test *P*-value<0.00001			
Race/ethnicity			
White	95.8 (95.0–96.4)	85.0 (83.6–86.2)	81.5 (80.0–82.9)
Black	91.8 (88.4–94.2)	74.4 (69.4–78.8)	70.7 (65.3–75.4)
Hispanic	93.9 (93.2–94.5)	79.0 (77.8–80.2)	74.4 (73.0–75.7)
Asian	94.4 (92.6–95.8)	81.4 (78.3–84.0)	77.4 (74.0–80.4)
Log-rank test *P*-value<0.00001			
Gender			
Male	94.3 (93.7–94.9)	79.5 (78.3–80.6)	75.1 (73.8–76.3)
Female	94.7 (94.0–95.4)	83.5 (82.2–84.7)	79.9 (78.4–81.2)
Log-rank test *P*-value<0.00001			
Leukemia immunophenotype			
B-cell	95.4 (94.8–95.9)	82.7 (81.6–83.7)	77.8 (76.5–79.0)
T-cell	90.8 (88.9–92.3)	73.8 (71.0–76.3)	71.0 (68.0–73.7)
NOS	94.3 (93.3–95.1)	81.1 (79.5–82.6)	77.8 (76.1–79.4)
Log-rank test *P*-value<0.00001			
Calendar period			
1988–1995	93.0 (91.9–93.9)	76.9 (75.2–78.5)	72.8 (71.1–74.5)
1996–2003	94.8 (93.9–95.5)	80.7 (79.3–82.1)	76.7 (75.1–78.1)
2004–2011	95.5 (94.7–96.1)	85.7 (84.3–87.0)	N/A

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Covariates	1-year survival (95%CI)	5-year survival (95%CI)	10-year survival (95%CI)
Log-rank test *P*-value<0.00001			
Socioeconomic status			
1. Lowest 20%	93.5 (92.4–94.4)	77.0 (75.3–78.7)	72.5 (70.5–74.3)
2	94.5 (93.4–95.5)	81.5 (79.6–83.2)	77.8 (75.6–79.6)
3	94.5 (93.3–95.4)	82.3 (80.3–84.1)	78.4 (76.2–80.5)
4	95.3 (94.1–96.2)	82.2 (80.1–84.1)	78.2 (75.9–80.3)
5. Highest 20%	95.5 (94.3–96.4)	85.4 (83.3–87.1)	81.3 (78.9–81.6)
Log-rank test *P*-value<0.00001			
Treatment at a pediatric cancer center			
No	92.9 (91.9–93.8)	77.0 (75.4–78.6)	73.2 (71.4–74.9)
Yes	95.2 (94.7–95.7)	83.0 (82.0–84.0)	78.9 (77.7–80.0)
Log-rank test *P*-value = 0.0014			
Type of health insurance: limited to cases diagnosed from 1996 onwards (N = 6638)			
No insurance	93.3 (88.1–96.9)	77.6 (68.9–84.1)	74.2 (64.4–81.6)
Private insurance	96.6 (94.9–96.2)	85.2 (83.9–86.4)	81.8 (80.3–83.2)
Public insurance	94.8 (93.9–96.5)	81.5 (79.9–83.1)	76.3 (74.3–78.3)
Unknown	91.6 (87.0–94.6)	66.2 (59.3–72.2)	63.0 (55.8–69.3)
Log-rank test *P*-value<0.00001			

CI, confidence interval; NOS, not otherwise specified; N/A, not applicable.

TABLE III.

Unadjusted and Multivariable-Adjusted Hazard Ratios and 95% Confidence Intervals for Overall Survival in Children (0–19 Years Old) With Acute Lymphoblastic Leukemia in California.

Covariates	Death N (%)	Unadjusted HR1 (1988–2011) (95%CI)	Adjusted HR2 (1988–2011) (95%CI)	Adjusted HR3 (1996–2011) (95%CI)	Adjusted HR4 (1996–2011) (95%CI)
Race/ethnicity					
White	568 (29.1)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Black	100 (5.1)	1.78 (1.44–2.20)	1.57 (1.26–1.96)	1.74 (1.31–2.31)	1.72 (1.29–2.28)
Hispanic	1,123 (57.4)	1.47 (1.33–1.62)	1.38 (1.23–1.55)	1.43 (1.22–1.68)	1.37 (1.17–1.62)
Asian	164 (8.4)	1.26 (1.06–1.50)	1.33 (1.12–1.59)	1.42 (1.13–1.79)	1.40 (1.11–1.76)
Gender					
Male	1,237 (63.3)	1.27 (1.16–1.39)	1.19 (1.09–1.31)	1.20 (1.06–1.35)	1.19 (1.06–1.35)
Female	718 (36.7)	1.0 (Reference)	1.0 (Reference)	1.00 (Reference)	1.00 (Reference)
Socioeconomic status					
1.Lowest 20%	623 (32.3)	1.61 (1.39–1.87)	1.39 (1.18–1.64)	1.40 (1.12–1.75)	1.30 (1.04–2.27)
2.	414 (21.2)	1.29 (1.10–1.51)	1.15 (0.97–1.35)	1.20 (0.95–1.51)	1.15 (0.91–1.44)
3.	339 (17.3)	1.20 (1.02–1.41)	1.13 (0.95–1.33)	1.10 (0.87–1.38)	1.06 (0.84–1.34)
4.	324 (16.6)	1.23 (1.04–1.45)	1.17 (0.99–1.39)	1.22 (0.97–1.54)	1.20 (0.95–1.51)
5. Highest 20%	246 (12.6)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Calendar period					
1988–1995	781 (39.9)	1.66 (1.47–1.87)	1.97 (1.74–2.24)	N/A	N/A
1996–2003	744 (38.1)	1.38 (1.22–1.56)	1.50 (1.33–1.70)	1.52 (1.34–1.73)	1.50 (1.33–1.71)
2004–2011	430 (22.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Treatment at a pediatric cancer center					
No	724 (37.0)	1.35 (1.23–1.48)	1.06 (0.96–1.16)	1.05 (0.92–1.19)	1.05 (0.92–1.19)
Yes	1,231 (63.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Type of health insurance: model limited to cases diagnosed from 1996 onwards (N = 6638)					
No insurance	29 (2.5)	1.54 (1.06–2.23)	N/A	N/A	1.22 (0.83–1.89)
Private insurance	583 (49.6)	1.00 (Reference)	N/A	N/A	1.00 (Reference)
Public insurance	487 (41.5)	1.31 (1.16–1.47)	N/A	N/A	1.15 (1.01–1.32)
Unknown	75 (6.4)	2.31 (1.82–2.94)	N/A	N/A	1.77 (1.38–2.26)

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified. The multivariable models were adjusted for all variables presented in the table and stratified by age, immunophenotype and secondary neoplasm. HR1, unadjusted model; Hr2, adjusted model without insurance, 1988–2011; Hr3, adjusted model without insurance, 1996–2011; Hr4, adjusted model with insurance, 1996–2011.